The endoplasmic reticulum chaperone protein GRP94 is required for maintaining hematopoietic stem cell interactions with the adult bone marrow niche.

Journal: PLoS One

Publication Year: 2011

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PubMed link: 21647226

Funding Grants: CIRM Stem Cell Biology Training Grant

Public Summary:
We identified GRP94 as a novel regulator of hematopoietic stem cells physiology and their interaction with the niche.

Scientific Abstract:
Hematopoietic stem cell (HSC) homeostasis in the adult bone marrow (BM) is regulated by both intrinsic gene expression products and interactions with extrinsic factors in the HSC niche. GRP94, an endoplasmic reticulum chaperone, has been reported to be essential for the expression of specific integrins and to selectively regulate early T and B lymphopoiesis. In GRP94 deficient BM chimeras, multipotent hematopoietic progenitors persisted and even increased, however, the mechanism is not well understood. Here we employed a conditional knockout (KO) strategy to acutely eliminate GRP94 in the hematopoietic system. We observed an increase in HSCs and granulocyte-monocyte progenitors in the Grp94 KO BM, correlating with an increased number of colony forming units. Cell cycle analysis revealed that a loss of quiescence and an increase in proliferation led to an increase in Grp94 KO HSCs. This expansion of the HSC pool can be attributed to the impaired interaction of HSCs with the niche, evidenced by enhanced HSC mobilization and severely compromised homing and lodging ability of primitive hematopoietic cells. Transplanting wild-type (WT) hematopoietic cells into a GRP94 null microenvironment yielded a normal hematology profile and comparable numbers of HSCs as compared to WT control, suggesting that GRP94 in HSCs, but not niche cells, is required for maintaining HSC homeostasis. Investigating this, we further determined that there was a near complete loss of integrin alpha4 expression on the cell surface of Grp94 KO HSCs, which showed impaired binding with fibronectin, an extracellular matrix molecule known to play a role in mediating HSC-niche interactions. Furthermore, the Grp94 KO mice displayed altered myeloid and lymphoid differentiation. Collectively, our studies establish GRP94 as a novel cell intrinsic factor required to maintain the interaction of HSCs with their niche, and thus regulate their physiology.